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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,668	08/28/2003	Alexei Brooun	SYR-ISPA-5001-CI	9129
32793	7590	10/24/2007	EXAMINER	
TAKEDA SAN DIEGO, INC. 10410 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121			KIM, ALEXANDER D	
ART UNIT		PAPER NUMBER		
1656				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/651,668	BROOUN ET AL.
	Examiner	Art Unit
	Alexander D. Kim	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 06 August 2007.
- 2a) This action is **FINAL**.                                   2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,4,6,9,10 and 18-24 is/are pending in the application.
  - 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) 19 and 24 is/are allowed.
- 6) Claim(s) 1,4,6,9,10,18 and 20-23 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) Notice of Informal Patent Application
- 6) Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action, a non-Final rejection (mailed on 04/05/2007), Applicants filed a response and amendment received on 08/06/2007. Said amendment cancelled Claims 2-3, 5, 7-8 and 11-17; amended Claims 1, 9 and 19; and newly added Claim 24.

Claims 1, 4, 6, 9-10 and 18-24 are pending in the instant Office action.

Thus, Claims 1, 4, 6, 9-10 and 18-24 will be examined herein.

### ***Withdrawn-Objections to the Specification***

2. The previous objection of specification inappropriate use of SEQ ID NOs and number of residues that do not corresponds to the SEQ ID NOs is withdrawn by virtue of Applicants' argument.

3. The previous objection of specification because of potential typographical error in the Oath and Declaration is withdrawn by virtue of Applicants' argument.

### ***Maintained-Objections to the Specification***

4. The previous objection of specification because it is unclear which protein is used in the actual crystallization in the Example 2 is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the instant objection is moot in view of Applicants' previous amendment of paragraph [00178] and [00183]. The recited amendment is clear that the polypeptide consisting of residues 1-314 of SEQ ID NO: 1 was appears to be used in the Example 2. However, it is unclear why Figure 3 representing the coordinates of instant ISP protein crystal has amino acid sequence of 16-314 of SEQ ID NO: 1, which is truncated form. Appropriate clarification is required.

***Withdrawn-Objections to the Drawing***

5. The previous objection to the Drawing because the corrected drawing filed on 07/05/2006 is missing pages at the end compared to the original Figure 3 is withdrawn by virtue of Applicants' amendment.

***Withdrawn-Claim Rejections - 35 USC § 112***

6. The previous rejection of Claim 16 (Claims 1 and 4 dependent therefrom) rejected under of 35 U.S.C. 112, second paragraph, is withdrawn by virtue of its cancellation.

7. The previous rejection of Claim 19 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' amendment.

8. The previous rejection of Claim 19 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants' amendment.

***Maintained-Claim Rejections - 35 USC § 112***

9. Claims 1, 4, 6, 9-10, 18 and 20-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 1, 4, 6, 9-10, 16 and 18-23. In response to this rejection, applicants have cancelled Claims 2-3, 5, 7-8 and 11-17; amended Claims 1, 9 and 19; and newly added Claim 24; and traverse the rejection as it applies to the newly amended claims.

Applicants argue disclosed species of co-crystal adequately describing a representative number of species, which does not require the description of every individual species within the claimed genus by the following reasons. Applicants argue "conditions to grow crystal became routine, particularly in the industry" and a skilled artisan would have been more capable of arriving at the conditions for crystallization of a protein consisting of "residues 1-314 of SEQ ID NO: 1"; thus, it was not necessary to disclose each and every condition, foreseeable or unforeseeable. Applicants further argue, because the instant method undertaken systematic broad screening crystallization trials on an IspA complex using the sitting drop techniques to obtain conditions that appear to produce precipitate and/or crystals, it led to a thorough understanding of how crystallization conditions affect IspA crystallization which is

summarized in Table 8 and further discloses in detailed crystallization condition in Example 2. Applicants also argue a protein crystallization method is a routine job in view of more than 30,000 publication prior to the filing date of the instant application. Thus, the species described in the instant specification describe claimed broad genus crystal (or co-crystal) or claimed genus method of crystallization sufficiently for one skilled in the art to possess the full scope of claims.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Examiner acknowledge that a patent application does not have to describe each and every species encompassed by the claims as long as disclosed species by the application or the prior art describe claimed genus sufficiently for one skilled in the art to possess the full scope of the claimed invention. Examiner acknowledge Applicants' argument stating, "a representative number is an inverse function of the skill and knowledge in the art", but one cannot ignore the representative number is also directly proportional to the scope of claimed invention. The breadth of claim 1 is drawn to a very widely varying composition comprising any crystal (including co-crystal if bound ligand is in the protein), wherein the crystal is consist of 1-314 of SEQ ID NO: 1 and the crystal has a crystal lattice in a P4<sub>1</sub>2<sub>2</sub> and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and  $\alpha=\beta=\gamma=90^\circ$ , wherein the composition includes any molecule (e.g., ligand(s)) or combination of molecules. Thus, one skilled in the art would not be able to possess the full scope of claimed invention by the virtue of instant disclosure lacking the disclosure of correlation between structure of composition and function of forming a protein crystal. The breadth of claim 6 is drawn

to a very widely varying method for forming a crystal of a protein (optionally), which is consist of 1-314 of SEQ ID NO: 1, in any suitable conditions encompassing unlimited mother liquor composition and their concentration as well as having unlimited molecule(s), compound(s) or any combination thereof. Thus, one skilled in the art would not be able to possess the full scope of claimed method by the virtue of instant disclosure lacking the disclosure of correlation between structure (i.e., a precipitant and a protein solution) and function (i.e., conditions suitable for forming a protein crystal when the suitable condition results in a protein crystal). The fact that there are many publication or disclosure of protein crystallization in general has very minimal (almost none) support for providing the representative species for the instant claims because every crystallization is case by case basis, specially those publication or disclosure is not about the crystallization of a protein consisting of residues 1-314 of SEQ ID NO: 1.

For the reasons above and the previous written description rejection, the instant rejection is maintained.

10. Claims 1, 4, 6, 9-10, 18 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a crystal or a method for preparing a co-crystal of a polypeptide consisting of residues 1-314 SEQ ID NO: 1 by a method of crystallizing a ternary complex consisting of said polypeptide with ligands (IPP+Risedronate, see specification page 49), that results in a crystal having the space group P4<sub>1</sub>2<sub>2</sub> and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and  $\alpha=\beta=\gamma=90^\circ$ , does not reasonably provide enablement for all crystals

and methods comprising the steps of using any suitable condition for the preparation of the co-crystal as broadly encompassed by the breadth claims.

The breadth of claim 1 is drawn to a very widely varying composition comprising any crystal (including co-crystal if bound ligand is in the protein), wherein the crystal is consist of 1-314 of SEQ ID NO: 1 and the crystal has a crystal lattice in a P4<sub>1</sub>2<sub>2</sub> and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and  $\alpha=\beta=\gamma=90^\circ$ , wherein the composition includes any molecule (e.g., ligand(s)) or combination of molecules. The breadth of claim 6 is drawn to a very widely varying method for forming a crystal of a protein (optionally), which is consist of 1-314 of SEQ ID NO: 1, in any suitable conditions encompassing unlimited mother liquor composition and their concentration as well as having unlimited molecule(s), compound(s) or any combination thereof.

The rejection was stated in the previous office action as it applied to previous Claims 1, 4, 6, 9-10, 16 and 18-23. In response to this rejection, applicants have cancelled Claims 2-3, 5, 7-8 and 11-17; amended Claims 1, 9 and 19; and newly added Claim 24; and traverse the rejection as it applies to the newly amended claims.

Applicants argue disclosed species of co-crystal adequately describing a representative number of species, which does not require the description of every individual species within the claimed genus by the following reasons. Applicants argue "conditions to grow crystal became routine, particularly in the industry" and a skilled artisan would have been more capable of arriving at the conditions for crystallization of a protein consisting of "residues 1-314 of SEQ ID NO: 1"; thus, it was not necessary to disclose each and every condition, foreseeable or unforeseeable. Applicants further

argue, because the instant method undertaken systematic broad screening crystallization trials on an IspA complex using the sitting drop techniques to obtain conditions that appear to produce precipitate and/or crystals, it led to a thorough understanding of how crystallization conditions affect IspA crystallization which is summarized in Table 8 and further discloses in detailed crystallization condition in Example 2. Applicants also argue a protein crystallization method is a routine job in view of more than 30,000 publication prior to the filing date of the instant application. Thus, the species described in the instant specification describe claimed broad genus crystal (or co-crystal) or claimed genus method of crystallization sufficiently for one skilled in the art to make and use the full scope of claims.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Examiner acknowledge that a patent application does not have to describe each and every species encompassed by the claims as long as disclosed species by the application or the prior art provide the describe claimed genus sufficiently for one skilled in the art to possess the full scope of the claimed invention. Examiner acknowledge Applicants' argument stating, "a representative number is an inverse function of the skill and knowledge in the art", but one cannot ignore the representative number is also directly proportional to the scope of claimed invention. Examiner also acknowledge that a routine experiment does not automatically require an undue experimentation. It is true that one skilled in the art can screen very widely varying crystallization condition using commercially available kit and robotic operation without undue experimentation. However, to make and use such screening

method to be a "conditions suitable for formation of a protein crystal" which encompasses a forming a crystal of a protein consist of residues 1-314 of SEQ ID NO: 1, would require a undue experimentation in view of very broad claimed crystal and/or claimed method of crystallization and unpredictability of forming protein crystal. The modernization of procedure do make the process of screening faster but does not decrease the unpredictability nature of protein crystallization. This very unpredictable nature of protein crystallization is the reason one skilled in the art first attempt to screen as broad crystallization conditions as possible, which is also supported by Applicants' own disclosure reciting the wide range of crystallization conditions disclosed by the present invention provide guidance to further explore for new conditions to grow the claimed crystal" (see bottom of page 8, Remark). The said further exploration is what makes one skilled in the art to require an undue experimentation for a protein crystallization, specially when the claims are drawn to a very widely varying genus as described above in the breadth of claims. Thus, the instant disclosure and the prior art failed to provide the guidance or direction to make and use the full scope of claimed invention without undue experimentation for one skilled in the art.

For the reasons above and the previous office action, the instant rejection is maintained.

#### ***Summary of Pending Issues***

11. The following is a summary of the issues pending in the instant application:

- (a) The previous objection of specification because it is unclear which protein is used in the actual crystallization in the Example 2 is maintained.
- (b) Claims 1, 4, 6, 9-10, 18 and 20-23 are stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- (c) Claims 1, 4, 6, 9-10, 18 and 20-23 are stand rejected under 35 U.S.C. 112, first paragraph, scope of enablement.

***Conclusion***

12. Claims 1, 4, 6, 9-10, 18 and 20-23 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim

October 12, 2007



RICHARD HUTSON, PH.D.  
PRIMARY EXAMINER